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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/035,223	01/04/2002	Yong Liang Chu	3781-002-27	3455

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EXAMINER	
AKHAVAN, RAMIN	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 09/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Applicants 09/20/04 BA

Office Action Summary	Application No.	Applicant(s)	
	10/035,223	CHU ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39 and 43-68* is/are pending in the application.

4a) Of the above claim(s) *1-32, 35-36 and 38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33,34,37,39 and 43-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *08/13/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgment is made of amendments, filed 0707/2004. Applicants have cancelled claims 40-42 and added new claims 43-68. Claims 1-32, 35-36 and 38 are withdrawn from consideration as drawn to nonelected subject matter. In addition, as noted in the previous Office Action, filed 04/07/2004, claims 33-34 and 37 are directed to non-elected subject matter (e.g. claim 33 and 37 are dependant from non-elected claim 1 and claim 34 recites "carbohydrate" which is also non-elected subject matter (i.e. Group III in the restriction requirement, filed 02/13/2004). Any objections/rejections not repeated herein are hereby withdrawn. Where applicable, arguments submitted with regard to objections/rejections maintained are addressed in the body of the rejections set forth below. Claims 33-34, 37, 39 and 43-68 are under consideration in this action. As no new grounds of rejection are set forth, **this action is FINAL**.

Response to Declaration filed under CFR 1.132

Applicants have submitted a declaration, filed 09/07/2004, providing a series of examples on how to make liposome formulations corresponding to the general formula of claim 43. (Declaration, Examples 1-8). In addition, there appears a single example demonstrating *in vitro* transfection of 293 and Hela cells, using a formulation of Dioctadecyl-(2-hydroxyl-3-propylamirio) aminopolylysine (DHPA) along with DOPE at a 1:1 ratio. (Declaration, Example 10). There is some ambiguity with respect to the information set forth in the Declaration. More particularly, Applicants appear to be asserting that two *in vitro* examples are set forth. (e.g. Declaration, Example 9). However, DHPA appears to be the only lipid that is set forth. (Declaration, Example 9, first sentence; reciting DHPA twice using the conjunction "or").

Claim Objections

Claims 33, 34 and 37 are objected to because of the following informalities: the claims are drawn in part to non-elected subject matter. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. **Claims 33-34, 37 and 39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.**

The claims contains subject matter, method of delivering any substance or genetic material *in vitro* or *in vivo*, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants' assertion that the disclosure contains sufficient information to enable one skilled in the art to make and use the invention recited without undue experimentation is not deemed persuasive, thus the rejection is maintained.

The test for enablement is whether one skilled in the art could make use the claimed invention from the disclosure in the specification coupled with information known in the art without undue experimentation. *United States v Telectronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor but instead is a conclusion reached by weighing many factors which are outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). The factors include the following:

Scope/Breadth of the claims. The claims are broad in the sense that the methods of introducing any substance are via a multitude of liposome formulations. Additional embodiments are directed to methods of introducing genetic material via an enormous number of liposome formulations as represented by the formula in claim 1. Moreover, the claims read on *in vitro* and *in vivo* gene transfer.

Nature of the invention. The invention involves transfer of any substance into cells using liposome formulations of claim 1 for both *in vitro* and *in vivo* transfer, each having attendant and distinct requirements. In so far as the claims read on *in vivo* transfer, the invention is drawn to a method of gene therapy using liposome formulations. Therefore the invention is drawn two categories of issues, the first being transfer of any substance *in vitro* (claims 33, 34, 37 and 39) and the second being genetic transfer *in vivo* which necessarily reads on gene therapy (claims 33, 34, 37, 39). The same concerns apply where the substance being transferred is genetic material (e.g. DNA or RNA).

State of the art/Unpredictability of the art. There is considerable overlap between the factors that affect transfer of genetic material into cells both *in vitro* and *in vivo*. This section will first address the state and unpredictability of the art, with respect to liposomal delivery of genetic material. Subsequently, the state and unpredictability of the art will be examined with respect to *in vivo* liposomal delivery of genetic material. Underpinning this examination is the finding that with respect to liposomal delivery, there is little correlation between *in vitro* results and *in vivo* application. (e.g. Templeton, DNA Cell Bio. 2002; 21(12):857-867, at p. 858, col. 1 bridging to col. 2).

There are a number of liposome formulations known in the art, but the lipid formulations, each comprising a compound with a distinct chemical formula, do not necessarily share common physiochemical and physiological characteristics. Indeed, liposomes have different morphologies based upon their composition and the formulation method. (Id. at p. 858, col. 2, last ¶). Some known lipid formulations are DOTMA, DOGS, DMRIE, DOSPA, DC-Chol and DOTAP. (See supra, Mahato et al. 1997, at p. 145). However, differing morphologies can affect whether transfer of a substance or transfer of genetic material is effectuated at all. *A priori* where the chemical nature of a lipid structure is altered, such a change will affect liposome formulation, which in turn can affect transfection efficiency (i.e. whether transfection or transfer occurs at all). For example, depending on the particular chemical formula and preparation method, the liposome formulation may inhere changes in charge density, for example, which would affect whether a substance is delivered at all.

Furthermore, liposome formulations are known to interact with cells via two major pathways, which are endocytosis and direct cell fusion, which in part depends on the liposome formulation charge density. The pathway selected may, with respect to particular formulations, determine whether efficient transfection occurs. (Id. at p. 861, col. 1; p. 862, Fig. 4). Moreover, altering the chemical structure of the lipids comprising the liposome formulation could affect the geometry of liposome formulations, which will differentially affect transfection efficiency. (e.g. Byk and Scherman. Drug Dev. Res. 2000; 50:566-72; at p. 567, col. 2). In sum, because physiochemical properties of lipids used to formulate liposomes may determine transfection efficiency, there would be a great deal of unpredictability in determining what particular lipid formulation would result in successful transfer of genetic material. (e.g. McCluskie et al.

Antisense Nuc. Acid Drug Dev. 1998; 8:401-14; at p. 410, col. 2, ¶ 4; indicating that size and charge properties may vary within a given lipid formulation affecting transfection efficiency). Put another way, the skilled artisan may know how to make a particular formulation, but would not be able to use the formulation without undue experimentation, in order to effectuate transfer of a substance into a cell, whether *in vitro* or *in vivo*.

Many of the same characteristics that are required for *in vitro* transfer of genetic material, also apply *in vivo* (i.e. physiochemical properties). As alluded to previously, *in vivo* transfer of genetic material necessarily reads on gene therapy. The level of unpredictability is understandably greater for *in vivo* liposome delivery of genetic material. Gene therapy is one of the most difficult areas of biology and medicine, and is still in a relatively nascent stage of development. Obstacles include poor efficiency of delivery of the transgene to the target cells, poor transformation efficiency of target cells, unpredictable, transient expression of the transgene in target cells and insertion of nucleic acids into non-target sites, etc. (See, Kmiec, American Scientist, 1999, Vol. 87: 240-147; Anderson, Nature, 1998, Vol. 392: 25-30; Verma et al., Nature, 1997, Vol. 389: 239-242; (reviewing the multitude of difficulties and lack of success in gene therapy methods); Check, Erika, Feb. 13, 2003, Nature, 421: 678 (citing occurrence of leukemia due to insertion of retroviral vectors used in gene therapy into a particular stretch of DNA); Juengst, ET. June 2003, BMJ, 326:1410-11 (indicating that gene transfer often has multiple and unpredictable effects on cells); supra, Templeton et al. 2002, at p. 861 (noting that non-targeted and even targeted delivery systems can be inefficient)). Moreover, in utilizing liposomes for gene delivery the unpredictability is further compounded by complications in attempting to target the liposome formulations to targeted cells. (Supra, Guo and Szoka. 2003, at

pp. 335-6; citing obstacles of liposome susceptibility to insult via plasma proteins, premature leakage, difficulty in transfer across subcellular barriers to reach intracellular cites and avoiding degradation).

Amount of guidance provided. Applicants have submitted several examples on how to make the lipid compounds of the invention and a single formulation, DHPA, as an example of *in vitro* transfer of genetic material into either 293 or Hela cells. However, there is little relevant guidance provided as to how to use the lipid formulations to effectuate transfer of any substance or transfer of genetic material either *in vivo*. Furthermore, given the enormous breadth of the lipid formulation encompassed by the claims, a single example of *in vitro* transfection, is deemed as little guidance.

Number of working examples. There do not appear to be any working examples presented relative to methods of delivering any substance or genetic material into cells, *in vivo*. Applicants have provided a single working example, in regard to transfection *in vitro*.

Level of Skill/Amount of Experimentation Required. The level of skill in the art required to practice the claimed invention is high. However, given the unsolved hurdles to successful practicing of the invention, the level of unpredictability in the art and lack of relevant working examples, and the enormous breadth of the compounds encompassed by the claims, it must be considered that the skilled artisan would necessarily be required to conduct trial and error experimentation of an undue nature in order to attempt to practice the claimed invention.

Response to Arguments

Applicants do not appear to rebut any of the assertions set for with respect to the *Wands* factors. It appears Applicants' only argument is that methods of delivery of lipid aggregates or

transfection are well known in the art. (Remarks, p. 19, bridging to p. 20). However, such a broad based assertion fails to take into consideration that the knowledge in the art was gained through substantial trial and error experimentation particular to specific formulations, whether with respect to *in vitro* or *in vivo* transfection. Applicants further assert that the working examples, as provided in the Declaration (filed 09/07/2004), provide a variety of liposome formulations that can be used to transfer a foreign substance into cells, but only a single lipid formulation is shown to work to transfer DNA. (See supra, Response to Declaration...). In sum, the disclosure does not provide sufficient information for one of ordinary skill in the art to make and use the invention corresponding to the full scope of the invention.

2. **Claims 43-68 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for Dioctadecyl-(2-hydroxyl-3-propylamino)aminopolylysine (DHPA), does not reasonably provide enablement for all lipid formulations encompassed by the claims.**

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The test for enablement is whether one skilled in the art could make use the claimed invention from the disclosure in the specification coupled with information known in the art without undue experimentation. *United States v Telectronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor but instead is a conclusion reached by weighing many factors which are outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

The same analysis/discussion as set forth above applies here in part (Supra, Enablement Rejection). The factors include the following:

Scope/Breadth of the claims. The claims are broad in the sense that the methods of introducing any substance are via a multitude of liposome formulations. Additional embodiments are directed to methods of introducing genetic material via an enormous number of lipid formulations as represented by the formula in claim 43.

Nature of the invention. The invention involves transfer of any substance into cells using liposome formulations of claim 43 for both *in vitro* transfer.

State of the art/Unpredictability of the art. There are a number of liposome formulations known in the art, each comprising a compound with a distinct chemical formula, which would not necessarily share common physiochemical and physiological characteristics as compared to other formulations. Indeed, liposomes have different morphologies based upon their composition and the formulation method. (Id. at p. 858, col. 2, last ¶). Some known lipid formulations are DOTMA, DOGS, DMRIE, DOSPA, DC-Chol and DOTAP. (See supra, Mahato et al. 1997, at p. 145). However, differing morphologies can affect whether transfer of a substance or transfer of genetic material is effectuated at all. *A priori* where the chemical nature of a lipid structure is altered, such a change will affect liposome formulation, which in turn can affect transfection efficiency (i.e. whether transfection or transfer occurs at all). For example, depending on the particular chemical formula and preparation method, the liposome formulation may inhere changes in charge density, for example, which would affect whether a substance is delivered at all.

Furthermore, liposome formulations are known to interact with cells via two major pathways, which are endocytosis and direct cell fusion, which in part depends on the liposome formulation charge density. The pathway selected may, with respect to particular formulations, determine whether efficient transfection occurs, (Id. at p. 861, col. 1; p. 862, Fig. 4) including any transfer at all. Moreover, altering the chemical structure of the lipids comprising the liposome formulation could affect the geometry of liposome formulations, which will differentially affect transfection efficiency. (e.g. Byk and Scherman. Drug Dev. Res. 2000; 50:566-72; at p. 567, col. 2). In sum, because physiochemical properties of lipids used to formulate liposomes may determine transfection efficiency, there would be a great deal of unpredictability in determining what particular lipid formulation would result in successful transfer of any substance or transfer of genetic material. (e.g. McCluskie et al. Antisense Nuc. Acid Drug Dev. 1998; 8:401-14; at p. 410, col. 2, ¶ 4; indicating that size and charge properties may vary within a given lipid formulation affecting transfection efficiency). Put another way, the skilled artisan may know how to make a particular formulation, but would not be able to use the formulation without undue experimentation, in order to effectuate transfer of a substance into a cell.

Amount of guidance provided. Applicants have submitted several examples on how to make the lipid compounds of the invention and a single formulation, DHPA, as an example of *in vitro* transfer of genetic material into either 293 or Hela cells. However, given the enormous breadth of the lipid formulation encompassed by the claims, a single example of *in vitro* transfection, the guidance provided is of value only insofar as providing an invitation for further experimentation.

Number of working examples. Applicants have provided a single working example, in regard to transfection *in vitro* (i.e. using DHPA to transfer plasmid DNA).

Level of Skill/Amount of Experimentation Required. The level of skill in the art required to practice the claimed invention is high. However, given the unsolved hurdles to successful practicing of the invention, the level of unpredictability in the art and lack of relevant working examples, and the enormous breadth of the compounds encompassed by the claims, it must be considered that the skilled artisan would necessarily be required to conduct trial and error experimentation of an undue nature in order to attempt to practice the claimed invention commensurate with the scope of the claims.

Conclusion

No claims are allowed. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ray Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached between 8:30-5:00, Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD, can be reached on 571-272-0781. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully submitted,

Ray Akhavan/AU 1636
09/20/04

GERRY LEFFERS
PRIMARY EXAMINER